

University of Groningen

Myocardial infarction and generalised anxiety disorder

Roest, Annelieke M.; Zuidersma, Marij; de Jonge, Peter

Published in:
British Journal of Psychiatry

DOI:
[10.1192/bjp.bp.111.103549](https://doi.org/10.1192/bjp.bp.111.103549)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2012

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Roest, A. M., Zuidersma, M., & de Jonge, P. (2012). Myocardial infarction and generalised anxiety disorder: 10-year follow-up. *British Journal of Psychiatry*, 200(4), 324-329. <https://doi.org/10.1192/bjp.bp.111.103549>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Generalized anxiety disorder after acute myocardial infarction as a predictor of cardiovascular events and all-cause mortality over 10 years

Annelieke M. Roest, Marij Zuidersma, Peter de Jonge

Word count: 2718

Short title: generalized anxiety disorder and outcomes after MI

Funding/Support

The DepreMI was funded by the Netherlands Organization for Scientific Research (Zon MW, grant 904-57-100).

Dr. de Jonge and drs. Zuidersma are supported by a VIDI grant from the Dutch Medical Research Council (grant 016.086.397).

There are no conflicts of interest.

Abstract

Background

Few studies have addressed the relationship between generalized anxiety disorder (GAD) and cardiovascular prognosis using a diagnostic interview.

Aim

To assess the association between GAD and adverse outcomes in myocardial infarction (MI) patients.

Method

Patients with acute MI (n=438) were recruited between 1997 and 2000 and were followed up until 2007. Current GAD and post-MI depression were assessed with the Composite International Diagnostic Interview. The endpoint consisted of all-cause mortality and cardiovascular related readmissions.

Results

During the follow-up period, 198 patients had an adverse event. GAD was associated with an increased rate of adverse events after adjustment for age and gender (hazard ratio: 1.94; 95% confidence interval: 1.14-3.30; p=0.01). Additional adjustment for measures of cardiac disease severity and depression did not change the results.

Conclusion

GAD was associated with an almost 2-fold increased risk of adverse outcomes independent from demographic and clinical variables and depression.

Key words: Generalized anxiety disorder, myocardial infarction, cardiovascular events, all-cause mortality

Introduction

During the last decades, substantial research has focused on the association between psychological distress and morbidity and mortality. Most studies have focused on the role of depression with coronary heart disease (CHD). Several meta-analyses indicate that depression is a risk factor for the development of CHD in the general population (1-3) and is associated with cardiovascular events and mortality in patients with CHD (3-6).

Less research has focused on the role of anxiety. A recent meta-analysis showed that symptoms of anxiety were associated with a 26% increased risk of incident CHD (7). Anxiety disorders have been shown to be associated to the development of CHD in a younger (8), and to all-cause mortality in an older male population (9). The results for generalized anxiety disorder (GAD) are inconsistent. GAD has been shown to be related to all-cause mortality in a veteran population (10). However, in a community sample of older persons, GAD did not increase the risk of death (11).

In patients with acute myocardial infarction (MI), the prevalence of elevated symptoms of anxiety is on average 30% (12). In a meta-analysis including 12 studies covering 5,750 MI patients, it was shown that anxiety is associated with a 36% increased risk of new cardiovascular events or mortality (12). A significant limitation of the studies focusing on the relationship between anxiety and impaired prognosis in MI patients conducted this far is that most have used questionnaires to assess the presence of elevated symptoms of anxiety. Although questionnaires can be used as screening tools (13-16) they are not sufficient to diagnose an anxiety disorder. Furthermore, questionnaires are inadequate in distinguishing between emotional disorders, specifically between anxiety and depression (13,17,18). To our knowledge, only three studies have assessed the association between GAD assessed with a diagnostic interview and adverse cardiovascular

prognosis. Two of these studies were in patients with (stable) CHD and found significant associations between GAD and cardiovascular events (13,19). In contrast, the third study concluded that acute coronary syndrome patients with a lifetime diagnosis of GAD tended to experience a better cardiac prognosis (20).

To date no study assessed the prognostic impact of a diagnosis of current GAD after acute MI. Therefore, we evaluated the prognostic impact of GAD after MI on new cardiovascular events and mortality up till 10 years after the MI using a formal diagnostic interview. As GAD and depression are closely associated (21-23) we specifically analyzed whether its impact is independent from depression.

Methods

Patients

Patients were included from the Depression after Myocardial Infarction (DepreMI) study. DepreMI was a naturalistic cohort study evaluating the effects of depression after MI on adverse cardiovascular outcomes. Details of this study are described elsewhere (24,25). Previous publications on DepreMI have all focused on the association between depression and cardiac disease (24-28). These studies found a significant association between depressive symptoms and incident depressive episodes with cardiovascular events after a 2.5 year follow-up period (26-28). The impact of anxiety on cardiovascular outcomes has not been examined before. Eligible patients admitted consecutively for MI at four hospitals in the Netherlands between September 1997 and September 2000 were asked to participate. At least two of the following three criteria for MI had to be met: 1) a documented increase in cardiac enzyme levels, 2) typical electrocardiographic changes, 3) at least 20 minutes of chest pain. Exclusion criteria were the presence of another somatic disease likely to influence short-term survival, MI during hospital admission for

another reason (except unstable angina), and being unable to participate in study procedures. The institutional review board of each participating hospital approved the protocol and all participants signed informed consent.

Assessment of GAD

GAD is characterized by a period of at least six months with prominent tension, worry and feelings of apprehension about every day events and problems. Associated symptoms are symptoms of autonomic arousal and other somatic or cognitive symptoms of tension and worry (29). The presence of an International Classification of Diseases (ICD)-10 diagnosis of current GAD was assessed by means of the Composite International Diagnostic Interview (CIDI) version 1.1 (30), which was administered 3 months post-MI in order to reduce possible confounding in the period surrounding the MI.

The ICD-10 criteria of GAD

- A. A period of at least six months with prominent tension, worry and feelings of apprehension, about every-day events and problems.
B. At least four symptoms out of the following list of items must be present, of which at least one from items (1) to (4).

Autonomic arousal symptoms

- (1) Palpitations or pounding heart, or accelerated heart rate.
- (2) Sweating.
- (3) Trembling or shaking.
- (4) Dry mouth.

Symptoms concerning chest and abdomen

- (5) Difficulty breathing.
- (6) Feeling of choking.
- (7) Chest pain or discomfort.
- (8) Nausea or abdominal distress.

Symptoms concerning brain and mind

- (9) Feeling dizzy, unsteady, faint or light-headed.
- (10) Feelings that objects are unreal, or that one's self is distant or "not really here".
- (11) Fear of losing control, going crazy, or passing out.
- (12) Fear of dying.

General symptoms

- (13) Hot flushes or cold chills.
- (14) Numbness or tingling sensations.

Symptoms of tension

- (15) Muscle tension or aches and pains.
- (16) Restlessness and inability to relax.
- (17) Feeling keyed up, or on edge, or of mental tension.
- (18) A sensation of a lump in the throat, or difficulty with swallowing.

Other non-specific symptoms

- (19) Exaggerated response to minor surprises or being startled.
- (20) Difficulty in concentrating, or mind going blank, because of worrying or anxiety.
- (21) Persistent irritability.
- (22) Difficulty getting to sleep because of worrying.

Assessment of the covariates

Age, gender, clinical characteristics, cardiac risk factors, and comorbidities were assessed during hospitalization for the index-MI and from hospital charts. Left ventricular ejection fraction (LVEF) was assessed by echocardiography, radionuclide ventriculography, gated single photon emission computed tomography, magnetic resonance imaging, angiography or clinical assessment. Living alone and level of education were assessed in an interview 3 months after the MI. The presence of an ICD-10 diagnosis of a post-MI depressive episode was assessed with the CIDI at 3 months after the MI.

Assessment of adverse outcomes

Data concerning mortality were obtained up till 31 December 2007 from the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. Data concerning hospital admissions in the period between the index-MI and 31 December 2007 came from the Dutch national registry of hospital discharges and were obtained from the Dutch Central Bureau of Statistics by linkage to the municipal personal records database. Hospital readmissions with ICD-9 codes 410, 411, 413, 414 (ischemic heart disease), 427.1, 427.4, 427.5 (cardiac arrhythmia), 428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 (heart failure), 433, 434, 435, 437.0, 437.1 (cerebrovascular disease) and 440, 443.9 (peripheral vascular disease) were included as cardiovascular events. We included these events so to be consistent with previous publications on this cohort (26-28). Primary endpoint of this study was a combined endpoint of cardiovascular events and all-cause mortality. The follow-up period for adverse outcomes started at the CIDI interview at 3 months after the MI and ended at 31 December 2007. This timeframe was chosen to optimize the number of potential events. Only deaths and cardiovascular related readmissions occurring

between the CIDI interview at 3 months after the MI and 31 December 2007 were considered as adverse outcomes.

Statistical analyses

Baseline demographic and clinical characteristics were compared with Chi-square and student t-test. For this purpose, non-normally distributed continuous variables were log-transformed. We calculated event-free survival-time as time to first event or death. If no event or death occurred, the patient was censored at 31 December 2007. Using Cox regression we evaluated whether event-free survival was different for patients with and patients without GAD after the MI. In the basic model, adjustments were made for age and gender. Additionally, we adjusted for LVEF, and diagnosis of post-MI depression, because these have been shown to be associated with worse cardiovascular prognosis. In sensitivity analyses, adjustments were made for other clinical variables that significantly predicted cardiovascular events and mortality in the present sample, namely anterior site of the index MI, and history of MI and peripheral vascular disease. For all analyses, SPSS 14 was used and significance level was set at 0.05, two-tailed.

Results

For this study, 1,166 patients were assessed for eligibility. Of these, 882 patients were eligible of whom 528 (59.9%) signed an informed consent. Of the 461 patients with a CIDI interview, 23 were excluded due to missing information on the endpoint, leaving 438 patients included for further analyses.

Generalized anxiety disorder

Three months after the index MI, 24 patients (5.5%) met the criteria for GAD. Patients with GAD were less likely to be treated with percutaneous transluminal coronary angioplasty ($p=0.03$) and more likely to have a history of MI ($p=0.02$) compared with patients without GAD. Of the patients with GAD, 12 (50%) had a concurrent depressive episode (table 1).

INSERT TABLE 1 HERE

During follow-up, 15 (62.5%) patients with GAD had a cardiovascular event or died compared with 183 (44.2%) patients without GAD (figure 1).

INSERT FIGURE 1 HERE

Predictors of cardiovascular events and mortality

During the follow-up period, 198 patients met the combined endpoint of all-cause mortality and cardiovascular events with a mean (standard deviation) follow-up period of 5.7 (3.1) years. Patients who had an event during the follow-up period were more likely to be older ($p<.001$), living alone ($p=0.04$), to have an anterior MI, ($p=0.02$), a LVEF lower than 40 ($p<.001$), and a history of MI ($p=0.001$), cerebrovascular disease ($p=0.01$) and peripheral vascular disease ($p<.001$) (table 2).

INSERT TABLE 2 HERE

GAD as predictor of cardiovascular events and mortality

Table 3 shows the association of GAD with adverse prognosis for different models. GAD was associated with cardiovascular events and mortality after adjustment for age and gender (figure 2).

INSERT FIGURE 2 HERE

After additional adjustment for LVEF, GAD remained an independent predictor of adverse outcome. LVEF (hazard ratio (HR): 1.58; 95% confidence interval (CI): 1.17-2.14; $p=0.003$) and age (HR per year: 1.03; 95% CI: 1.02-1.04, $p<.001$) were also significant predictors in this model. Adjustment for post MI depression did not affect the association between GAD and cardiovascular events and mortality. Post-MI depression was not a significant predictor of adverse outcome in this model (HR: 1.20 95% CI: 0.80-1.80, $p=0.38$).

INSERT TABLE 3 HERE

In sensitivity analyses, in addition to age and gender, consecutive adjustment for history of MI, history of peripheral vascular disease, and anterior site of the index MI did not materially affect the association between GAD and adverse prognosis (table 3).

Discussion

This study is the first to assess the prognostic impact of a diagnosis of current GAD following MI on cardiovascular events and all-cause mortality up till 10 years. Patients with GAD were at an almost two-fold increased risk of adverse prognosis after adjustment for age, gender, and several cardiac disease severity parameters. Our findings are in concordance with those of other studies that investigated the impact of GAD in patients with stable heart disease (13,19). In the present study, adjustment for

depression did not influence the association of GAD with adverse prognosis. This is consistent with other studies assessing the association between anxiety and cardiovascular events independent from depression (19,31).

Potential mechanisms

Several potential biological mechanisms might explain the association between GAD and CHD. For instance, several studies found a relationship between anxiety and indicators of autonomic dysfunction in MI patients, including reduced heart variability (32) and reduced baroreflex cardiac control (33). Anxiety is also associated with increased platelet activity (34) and markers of inflammation (35), in otherwise healthy individuals. Another mechanism that may explain the association between anxiety and CHD is unhealthy behavior, like physical inactivity, an unhealthy diet, and smoking. Anxiety is related to an unhealthy lifestyle in individuals at risk of CHD (36). In addition, anxiety following MI is associated with lower adherence to various risk-reducing recommendations, such as smoking cessation (37,38). However, in a recent study, a variety of potential mediating mechanisms, including levels of cortisol and norepinephrine, heart rate variability, inflammation, smoking, medication nonadherence, and physical inactivity, could not explain the association between GAD and cardiovascular events in patients with stable CHD (19). More research is needed to identify the mechanisms through which GAD leads to an adverse prognosis.

Strengths and limitations

Strength of the present study is the use of a standardized diagnostic interview to assess the presence of GAD in this sample of patients with acute MI. Other strengths are the long follow-up period and the objective and comprehensive assessment of cardiovascular related readmissions and mortality, resulting in a sufficient number of

events. Limitations of this study are that we did not have information on the duration of the current GAD period or information on whether patients were treated for GAD or depression. In addition, we could not take the possible development of new GAD or depressive episodes during the time frame of the follow-up period into account. Another limitation is the relatively small sample size, which limits our ability to adjust for potential covariates simultaneously. An additional limitation resulting from the relatively small sample size is that we could not assess the impact of the comorbidity of GAD and depression. It has been suggested that GAD and depression might interact synergistically to affect cardiovascular mortality (10). However, in a study in patients with stable CHD, those with comorbid depression and GAD were not at a greater risk of cardiovascular events compared with those with only depression or GAD (13). Further, another large population study found that comorbid anxiety symptoms reduced mortality compared with depressive symptoms alone (39). Therefore, more research to the impact of comorbid anxiety and depression on the development and progression of CHD is warranted.

In the present study, the association between GAD and adverse prognosis could not be explained by several cardiac disease severity parameters, including LVEF and anterior site of the index MI. However, it is still possible that the association is confounded by disease severity, especially since some symptoms of GAD, such as palpitations and chest pain, might also be symptoms of heart disease. Further, patients with GAD might worry about their health and be more likely to consult their doctor and be admitted to the hospital with cardiac complaints. This might explain part of the association between GAD and cardiovascular related hospital readmissions. To minimize this effect, we excluded hospital admissions for chest pain only from our analyses. Furthermore, although

analyses on mortality separate from cardiovascular events were underpowered, the HR suggested an adverse effect of GAD on mortality alone as well (data not shown).

Clinical implications

Although it has not been specifically studied in patients with heart disease, GAD can be effectively treated with psychopharmacological treatment, e.g. selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, and cognitive behavioral therapy (40). Unfortunately, many patients do not receive adequate treatment (40). Besides the impact of anxiety on disability and decreased quality of life, clinicians should be aware of the finding that GAD is associated with an increased risk of cardiovascular events and mortality following MI.

In summary, this study showed that in patients with acute MI, GAD was associated with an almost 2 fold increased risk of new cardiovascular events and mortality. This association remained significant after adjustment for age, gender, measures of disease severity and depression. More research is needed to identify the mechanisms through which GAD is associated with an adverse prognosis following MI.

References

1. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med* 2003; **65**: 201-10.
2. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry* 2007; **22**: 613-26.
3. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006; **27**: 2763-74.
4. Van Melle JP, De Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004; **66**: 814-22.
5. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004; **66**: 802-13.
6. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry* 2011; **33**: 203-16.
7. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease. *J Am Coll Cardiol* 2010; **56**: 38-46.

8. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. *J Am Coll Cardiol* 2010; **56**: 31-7.
9. Van Hout HP, Beekman AT, de Beurs E, Comijs H, van Marwijk H, de Haan M, et al. Anxiety and the risk of death in older men and women. *Br J Psychiatry* 2004; **185**: 399-404.
10. Phillips AC, Batty GD, Gale CR, Deary IJ, Osborn D, MacIntyre K, et al. Generalized anxiety disorder, major depressive disorder, and their comorbidity as predictors of all-cause and cardiovascular mortality: the Vietnam experience study. *Psychosom Med* 2009; **71**: 395-403.
11. Holwerda TJ, Schoevers RA, Dekker J, Deeg DJ, Jonker C, Beekman AT. The relationship between generalized anxiety disorder, depression and mortality in old age. *Int J Geriatr Psychiatry* 2007; **22**: 241-9.
12. Roest AM, Martens EJ, Denollet J, de Jonge P. Prognostic association of anxiety post myocardial infarction with mortality and new cardiac events: a meta-analysis. *Psychosom Med* 2010; **72**: 563-9.
13. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry* 2008; **65**: 62-71.
14. Brennan C, Worrall-Davies A, McMillan D, Gilbody S, House A. The Hospital Anxiety and Depression Scale: a diagnostic meta-analysis of case-finding ability. *J Psychosom Res* 2010; **69**: 371-8.
15. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007; **146**: 317-25.

16. Kroenke K, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry* 2010; **32**: 345-59.
17. Balon R. Measuring anxiety: are we getting what we need? *Depress Anxiety* 2005; **22**: 1-10.
18. Beuke CJ, Fischer R, McDowall J. Anxiety and depression: why and how to measure their separate effects. *Clin Psychol Rev* 2003; **23**: 831-848.
19. Martens EJ, de Jonge P, Na B, Cohen BE, Lett H, Whooley MA. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease. *Arch Gen Psychiatry* 2010; **67**: 750-8.
20. Parker GB, Owen CA, Brotchie HL, Hyett MP. The impact of differing anxiety disorders on outcome following an acute coronary syndrome: time to start worrying? *Depress Anxiety* 2010; **27**: 302-9.
21. Krueger RF. The structure of common mental disorders. *Arch Gen Psychiatry* 1999; **56**: 921-926.
22. Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS study. *Arch Gen Psychiatry* 2001; **58**: 597-603.
23. Lamers F, van Oppen P, Comijs HC, Smit JH, Spinhoven P, van Balkom AJ, et al. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry* 2011; **72**: 341-8.
24. Spijkerman T, de Jonge P, van den Brink RH, Jansen JH, May JF, Crijns HJ, et al. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. *Gen Hosp Psychiatry* 2005; **27**: 411-7.

25. Spijkerman TA, van den Brink RH, Jansen JH, Crijns HJ, Ormel J. Who is at risk of post-MI depressive symptoms? *J Psychosom Res* 2005; **58**: 425-32.
26. Spijkerman TA, van den Brink RH, May JF, Winter JB, van Melle JP, de Jonge P, et al. Decreased impact of post-myocardial infarction depression on cardiac prognosis? *J Psychosom Res* 2006; **61**: 493-9.
27. Kaptein KI, de Jonge P, van den Brink RH, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: a latent class analysis. *Psychosom Med* 2006; **68**: 662-8.
28. de Jonge P, van den Brink RH, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol* 2006; **48**: 2204-8.
29. World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders Diagnostic Criteria for Research. Geneva: World Health Organization 1993.
30. Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res* 1994; **28**: 57-84.
31. Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J Am Coll Cardiol* 2003; **42**: 1801-7.
32. Martens EJ, Nyklíček I, Szsabó BM, Kupper N. Depression and anxiety as predictors of heart rate variability after myocardial infarction. *Psychol Med* 2008; **38**: 375-83.
33. Watkins LL, Blumenthal JA, Carney RM. Association of anxiety with reduced baroreflex cardiac control in patients after acute myocardial infarction. *Am Heart J* 2002; **143**: 460-6.

34. Cameron OG, Smith CB, Lee MA, Hollingsworth PJ, Hill EM, Curtis GC. Adrenergic status in anxiety disorders: platelet alpha 2-adrenergic receptor binding, blood pressure, pulse, and plasma catecholamines in panic and generalized anxiety disorder patients and in normal subjects. *Biol Psychiatry* 1990; **28**: 3-20.
35. Pitsavos C, Panagiotakos DB, Papageorgiou C, Tsetsekou E, Soldatos C, Stefanadis C. Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. *Atherosclerosis* 2006; **185**: 320-6.
36. Bonnet F, Irving K, Terra JL, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis* 2005; **178**: 339-44.
37. Benninghoven D, Kaduk A, Wiegand U, Specht T, Kunzendorf S, Jantschek G. Influence of anxiety on the course of heart disease after acute myocardial infarction – risk factor or protective function? *Psychother Psychosom* 2006; **75**: 56-61.
38. Kuhl EA, Fauerbach JA, Bush DE, Ziegelstein RC. Relation of anxiety and adherence to risk-reducing recommendations following myocardial infarction. *Am J Cardiol* 2009; **103**: 1629-34.
39. Mykletun A, Bjerkeset O, Overland S, Prince M, Dewey M, Stewart R. Levels of anxiety and depression as predictors of mortality: the HUNT study. *Br J Psychiatry* 2009; **195**: 118-25.
40. Davidson JR. First-line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatry* 2009; **70**: 25-31.

Figure 1

Title: Adverse outcomes in patients with and without GAD and depression

Caption:

Percentage of cardiac events and all-cause mortality in patients with versus without GAD and patients with versus without depression

GAD= generalized anxiety disorder

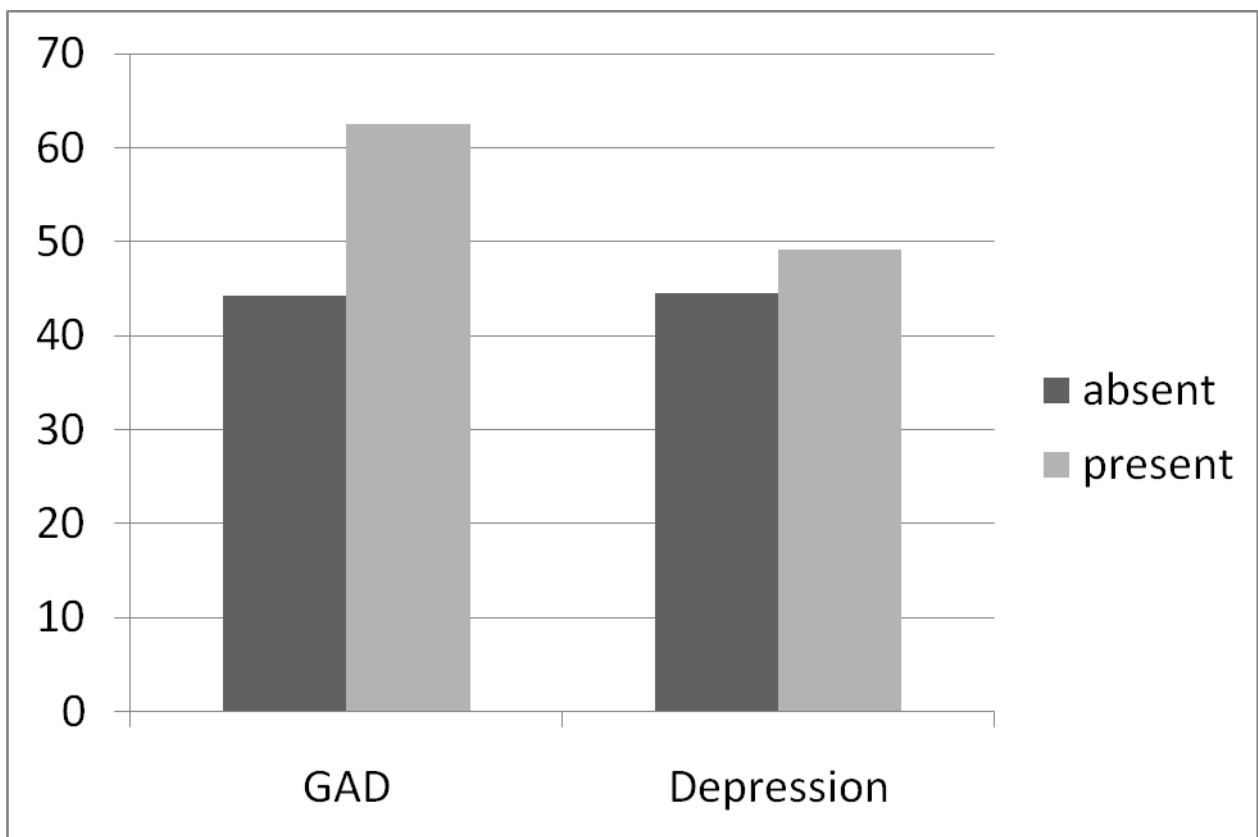


Figure 2

Title:

GAD and cardiac events and all-cause mortality

Caption:

The association of GAD after MI with cardiac events and all-cause mortality adjusted for age and gender

GAD= generalized anxiety disorder; MI= myocardial infarction

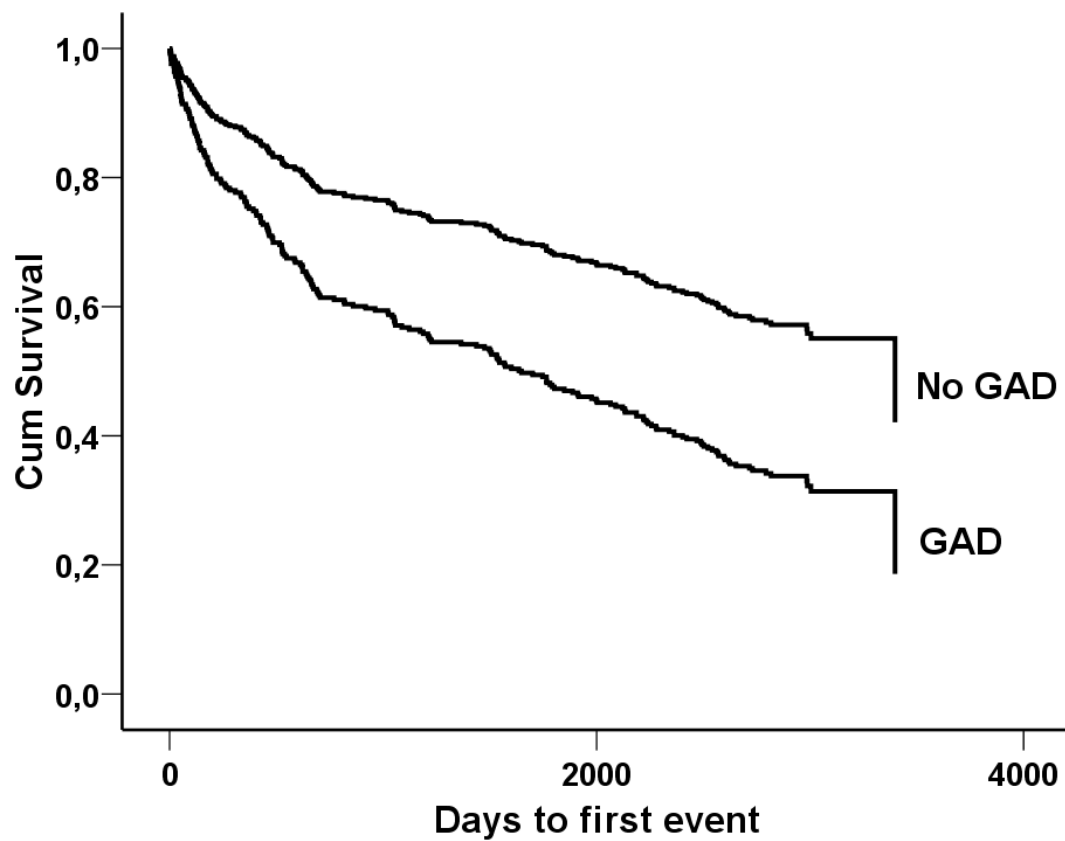


Table 1 Comparison of patients with and without GAD*

	No GAD (n=414)	GAD (n=24)	p
Age, years mean (sd)	60.7 (11.4)	58.3 (10.9)	0.33
Male gender n (%)	334 (80.7)	20 (83.3)	0.75
Primary school only n (%)	78 (18.8)	6 (25.0)	0.46
Living alone n (%)	58 (14.0)	5 (20.8)	0.35
Current smoking n (%)	194 (51.3)	14 (63.6)	0.26
LVEF <40 n (%)	97 (23.5)	7 (29.2)	0.53
Anterior site of MI n (%)	130 (31.4)	8 (33.3)	0.84
PTCA n (%)	100 (26.3)	1 (4.8)	0.03
CABG n (%)	12 (3.2)	2 (9.5)	0.12
Killip class ≥ 2 n (%)	13 (3.2)	2 (8.3)	0.18
CPK-mb mean (SD)†	117.8 (122.9)	121.7 (182.2)	0.16
CPK mean (SD)†	1322.8 (1319.2)	1818.9 (3010.8)	0.48
History of MI n (%)	53 (12.8)	7 (29.2)	0.02
History of cerebral vascular disease n (%)	18 (4.3)	1 (4.2)	0.97
History of peripheral vascular disease n (%)	27 (6.5)	3 (12.5)	0.26
Family history of cardiovascular disease n (%)	155 (37.4)	9 (37.5)	1.00
Diabetes n (%)	37 (8.9)	4 (16.7)	0.21
Hypertension n (%)	118 (28.5)	3 (12.5)	0.09

Hypercholesterolemia n (%)	144 (34.8)	7 (29.2)	0.57
Body mass index (sd)	26.7 (4.0)	26.8 (4.1)	0.92
Depression n (%)	53 (12.8)	12 (50.0)	<.001
History of depression (including post-MI depression) (%)	75 (18.1)	12 (50.0)	<.001

*t-test for continuous variables and Chi-square for dichotomous variables were used

†Log-transformations of CPK were used for the t-test

CABG= coronary artery bypass graft; CPK= creatinine phosphokinase; GAD= generalized anxiety disorder; LVEF= left ventricular ejection fraction; MI= myocardial infarction; PTCA= percutaneous transluminal coronary angioplasty.

Table 2 Comparison of patients with and without an adverse prognosis*

	Total sample (n=438)	Event-free (n=240)	Adverse event (n=198)	p
Age, years mean (sd)	61 (11.4)	58 (10.8)	63 (11.5)	<.001
Male gender n (%)	354 (80.8)	198 (82.5)	156 (78.8)	0.33
Primary school only n (%)	84 (19.2)	42 (17.5)	42 (21.2)	0.33
Living alone n (%)	63 (14.4)	27 (11.3)	36 (18.2)	0.04
Current smoking n (%)	208 (52.0)	114 (51.1)	94 (53.1)	0.69
LVEF <40 n (%)	104 (23.8)	40 (16.7)	64 (32.5)	<.001
Anterior site of MI n (%)	138 (31.5)	64 (26.7)	74 (37.4)	0.02
PTCA n (%)	101 (25.2)	61 (27.4)	40 (22.5)	0.26
CABG n (%)	14 (3.5)	10 (4.5)	4 (2.2)	0.23
Killip class ≥ 2 n (%)	15 (3.4)	6 (2.5)	9 (4.6)	0.24
CPK-mb mean (SD)†	118.0 (126.6)	117.9 (132.0)	118.1 (119.9)	0.75
CPK mean (SD)†	1350.0 (1461.0)	1347.2 (1523.8)	1353.3 (1384.9)	0.70
History of MI n (%)	60 (13.7)	21 (8.8)	39 (19.7)	0.001
History of cerebral vascular disease n (%)	19 (4.3)	5 (2.1)	14 (7.1)	0.01
History of peripheral vascular disease n (%)	30 (6.8)	7 (2.9)	23 (11.6)	<.001
Family history of cardiovascular disease n (%)	164 (37.4)	89 (37.1)	75 (37.9)	0.86

Diabetes n (%)	41 (9.4)	18 (7.5)	23 (11.6)	0.14
Hypertension n (%)	121 (27.6)	66 (27.5)	55 (27.8)	0.95
Hypercholesterolemia n (%)	151 (34.5)	80 (33.3)	71 (35.9)	0.58
Body mass index (sd)	26.7 (4.0)	26.7 (4.5)	26.7 (3.3)	0.98
Depression n (%)	65 (14.8)	33 (13.8)	32 (16.2)	0.48
GAD n (%)	24 (5.5)	9 (3.8)	15 (7.6)	0.08

* t-test for continuous variables and Chi-square for dichotomous variables were used

†Log-transformations of CPK were used for the t-test

CABG= coronary artery bypass graft; CPK= creatinine phosphokinase; GAD= generalized anxiety disorder; LVEF= left ventricular ejection fraction; MI= myocardial infarction; PTCA= percutaneous transluminal coronary angioplasty.

Table 3 Association of GAD with cardiac events and all-cause mortality

Controlling for:	HR (95% CI)	p
Age, gender	1.94 (1.14-3.30)	0.01
Age, gender, LVEF	1.92 (1.13-3.28)	0.02
Age, gender, depression	1.84 (1.06-3.17)	0.03
Age, gender, history of MI	1.81 (1.06-3.09)	0.03
Age, gender, history of peripheral vascular disease	1.95 (1.15-3.31)	0.01
Age, gender, anterior site of index MI	1.89 (1.11-3.22)	0.02

CI= confidence interval; GAD= generalized anxiety disorder; HR: hazard ratio; LVEF= left ventricular ejection fraction; MI= myocardial infarction.

Contributing authors

Annelieke M. Roest, MSc

Department of Psychiatry, University of Groningen, Groningen, The Netherlands.

Marij Zuidersma, MSc

Department of Psychiatry, University of Groningen, Groningen, The Netherlands.

Peter de Jonge, PhD

Department of Psychiatry, University of Groningen, Groningen, The Netherlands.

CoRPS – Center of Research on Psychology in Somatic diseases, Department of Medical Psychology, Tilburg University, Tilburg, The Netherlands

Address for correspondence:

Peter de Jonge

Department of Psychiatry

Hanzeplein 1, 9713 GZ Groningen, The Netherlands

E-mail p.de.jonge@med.umcg.nl

Fax +31 503619722

Phone +31 503619005

All authors have contributed substantially to the conception and design or analysis and interpretation of the data and to the draft and revising of the manuscript. All authors have read and approved the manuscript.